Design and synthesis of novel N-substituted morpholino benzamide derivatives as antimicrobial agents

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ABSTRACT

A mixture of 4-chloro benzonitrile and morpholine was subjected to microwave irradiation in solvent free condition to give 4-morpholino benzonitrile (1). Partial hydrolysis of (1) in 6N sodium hydroxide and 30% H2O2 resulted in 4-morpholino benzamide (2). A series of N-((2-hydroxynaphthalen-1-yl) (substituted phenyl) methyl)-4-morpholino benzamide 3 (a-k) was obtained in one pot synthesis by stirring 2 with aromatic aldehyde and β-naphthol in presence of oxalic acid as catalyst in solvent free condition. The synthesized compounds were evaluated for their antibacterial and antitubercular activity. Some of the synthesized compounds like 3b, 3g and 3k have shown excellent antibacterial activity against B. subtilis and S. aureus. Amongst the compounds tested 3f and 3h were found to be the potent against M. tuberculosis H37Rv.

INTRODUCTION

Microorganisms are exceptionally diverse, found almost everywhere and affect the human society in countless ways [1]. In particular, the emergence of multi-drug resistant strains of Gram-positive bacterial pathogens such as Methicillin-Resistant Staphylococcus aureus (MRSA) is a problem of ever-increasing significance [2, 3, 4]. Consequently, there is a vital need for the development of new antimicrobial agents having potent activity against the resistant microorganisms [5-8].

Naphthalene and its derivatives have shown a large spectrum of antimicrobial activity. Literature survey reveals that extensive research has been done on β-naphthol as an excellent lead moiety for designing a synthetic derivative, which posses good biologically activity [9-13]. Morpholine ring enhances the antimicrobial activity [14, 15], the marketed antibacterial drug Linezolid contains morpholine ring. In the present study, coupled synthetic derivatives containing β-naphthol, morpholine ring and aromatic aldehyde were synthesized and speculated to get enhanced bioactivity due to combined effect of these moieties. The development of pharmacophoric model is shown in Figure 1.
**Target Molecule**

*Figure 1 The development of pharmacophoric model for synthesized compound.*

**Chemistry**

N-((2-Hydroxynaphthalen-1-yl)(substitutedphenyl)methyl)-4-morpholinobenzamide derivatives 3(a-k) were synthesized as per the scheme of synthesis, **Scheme1**. Some of the reactions were carried out in synthetic microwave so as to get faster reaction rate and better yield.

**Scheme 1**

\[ \text{i = Solvent free, 25 min, (700 W) MW} \]
\[ \text{ii = NaOH/H}_2\text{O}_2, 4h, \text{stirring 40-50°C} \]
\[ \text{iii = Solvent free, oxalic acid, β-naphthol, Ar-CHO (8-24 min) stirring 125°C} \]

**Ar**

- a. 4-OCH$_3$C$_6$H$_4$
- b. 4-OH C$_6$H$_4$
- c. 4-CH$_2$C$_6$H$_4$
- d. furfuryl
- e. 2-SH C$_6$H$_4$
- f. 2-OH C$_6$H$_4$
- g. 4-ClC$_6$H$_4$
- h. 2,4-diCl C$_6$H$_3$
- i. NO$_2$C$_6$H$_4$
- j. 4-ph
- k. 4-FC$_6$H$_4$
4-Chlorobenzonitrile was reacted with morpholine to give 4-morpholinobenzonitrile I [15]. The reaction was carried out by two methods I) Conventional, II) Microwave-assisted. The comparison of the data obtained by these methods is given in Table 1.

Table 1: Physical characterization data for 4-morpholinobenzonitrile

<table>
<thead>
<tr>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>% Yield Method I</th>
<th>% Yield Method II</th>
<th>Time required Method I</th>
<th>M. P. (°C)</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅NCl</td>
<td>188</td>
<td>53.28</td>
<td>65.33</td>
<td>12 h 25 min</td>
<td>82-83°C</td>
<td>0.33</td>
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</table>

Table 2: Physical constants data for synthesized derivatives 3(a-k)

<table>
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<th>Sr. no.</th>
<th>R</th>
<th>Method I</th>
<th>Method II</th>
<th>Melting Point (°C)</th>
<th>Rf Value</th>
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<tbody>
<tr>
<td></td>
<td>% Yield</td>
<td>Time In hr</td>
<td>% Yield</td>
<td>Time In min</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>60.1</td>
<td>14</td>
<td>85.4</td>
<td>20</td>
<td>185-187</td>
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<tr>
<td>3b</td>
<td>65.2</td>
<td>13</td>
<td>88.9</td>
<td>24</td>
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<tr>
<td>3c</td>
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<td>16</td>
<td>80.1</td>
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<td>215-217</td>
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<tr>
<td>3d</td>
<td>59.2</td>
<td>16</td>
<td>82.4</td>
<td>16</td>
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<tr>
<td>3e</td>
<td>64.2</td>
<td>17</td>
<td>80.4</td>
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<tr>
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<td>84.1</td>
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<td>11</td>
<td>90.7</td>
<td>18</td>
<td>230-232</td>
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<tr>
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<td>73.3</td>
<td>11</td>
<td>94.1</td>
<td>8</td>
<td>180-182</td>
</tr>
</tbody>
</table>

Solvent system chosen for Rf value determination was n-hexane : ethyl acetate (4 : 1)

Method I= Stirring at room temperature with solvent
Method II= Stirring at 125°C without solvent

The intermediate compound 4-morpholinobenzamide 2 obtained by partial hydrolysis of 4-morpholinobenzonitrile using H₂O₂, NaOH [16]. The final compound N-((2-hydroxynaphthalen-1-yl)(substituted phenyl) methyl)-4-morpholinobenzamide 3(a-k) were synthesized by stirring at 125°C for 8-24 min without solvent in presence of catalytic amount of oxalic acid as described in general procedure [17]. All the compounds were identified by spectral data. In general, IR spectra in cm⁻¹ of 4-morpholinobenzonitrile (I) showed bands at 2226 (C-N nitrile), 3091(C-C aromatic ring) 2900 (C-H alicyclic) 1190 (C-N amine). The ¹H-NMR showed signals at δ3.18, δ3.65 (t, 2H, CH₂ morpholine ring) and δ7.46, δ6.94 (d, 2H, CH₂ benzene) MS m/z: 188 (M). The compound morpholino

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benzamide (2) exhibited bands at 3363-3182 (NH₂ amine), 3000 (C-H aromatic), 2900 (C-H aliphatic), 1657 (C=O amide), 1408 (C-N amide). The ¹H-NMR presented signals at 63.18, 83.65 (t, 2H, CH₂ morpholine ring), 86.94, 87.60 (d, 2H, CH₂ benzene), 87.50 (s, 2H, -CONH₂, D2O exchangeable). MS m/z: 207 (M). The assignments of the synthesized were based on elemental and spectral data. Physical characterization data of the synthesized derivatives is given in Table 2.

MATERIALS AND METHODS

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled unless otherwise noted. Synthetic microwave oven Cata R, was used for the first step of synthesis. Melting points were determined by open capillary method and are uncorrected. Infrared spectra were recorded on JASCO FT IR (PS-4000) using KBr powder technique and frequencies are expressed in cm⁻¹. Mass spectra were recorded on Micromass Q-Tof Micro system mass spectrometer. ¹H-NMR spectra were recorded on Varian Mercury 300 FT-NMR Spectrometer operating at 300 MHz (¹H) and on BRUKER AVANCE II 400 spectrometer operating at 400 MHz (¹H) in deuterated dimethyl sulfoxide. Chemical shifts are reported in ppm (d) relative to tetra methyl silane. Proton spectra were typically obtained at room temperature. Elemental analyses (C, H and N) were undertaken with a shimadzu s FLASHEA112 analyzer and all analyses were consistent with theoretical values (within ± 0.5%) unless indicated. For TLC, plates coated with silica gel were run in benzene/methanol, n-hexane/ethyl acetate mixture and spots were developed in iodine chamber. The anti-mycobacterial activities were evaluated against Mycobacterium Tuberculosis H37Rv using the tube dilution method. This methodology is nontoxic, uses a thermally- stable reagent. All the synthesized compounds were dissolved, separately, in dimethyl sulfoxide to prepare a stock solution containing 1000 µg/mL. The successive concentrations like 500, 200, 100, and 50 and µg/mL so on were prepared in a similar manner up to 6 dilutions. A sweep of Mycobacterial tuberculosis H37Rv strain culture was discharged with the help of 22 S.G.W. nichrome wire loop with a 3mm external diameter, into a sterile distilled bijou bottle containing six 3mm glass beads and 4 ml distilled water.

Antibacterial activity was assessed against B. subtilis (ATCC-6633) and S. aureus (ATCC-6538). MIC was determined using Cup-plate method. Test solution was prepared by dissolving 5 mg of the synthesized compound to 1 ml of sterile dimethyl sulphoxide (DMSO) to obtain a concentration of 5000 µg/ml. Each Petri dish containing Muller-Hinton agar medium was inoculated with one bacterial culture by spreading the suspension of the organism with a sterile glass beads. One cup was filled with 0.01 ml of standard drug i.e. linezolid, One was filled with 0.01 ml of DMSO; others were filled with 10 µl-40 µl (0.01-0.04 ml) of synthesized compound’s solution in sterile DMSO. All plates were kept in the refrigerator for 30 minutes to allow the diffusion of sample to the surrounding agar medium. The Petri dishes were incubated at 37°C for 24 hrs. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated.

In the present work total 11 derivatives of N-((2-hydroxynaphthalen-1-yl)(substitutedphenyl)methyl)-4-morpholinobenzamide 3(a-k) were synthesized.

All the compounds were identified by spectral data.

4.1 Synthesis of 4-morpholino benzonitrile (1)

I) Conventional Method: A mixture of morpholine (3 g, 34 mmol) and 4-chlorobenzonitrile (1.55 g, 11.2 mmol) were heated at 120°C. The conversion of the 4-chlorobenzonitrile was completed in 12 hours. Then water (10 ml) was added into the reaction mixture. Then precipitate was filtered off, washed with water and dried under vacuum (30 °C). The compound was recrystallized with 50% aqueous ethanol.

II) Microwave-assisted Method: A mixture of morpholine (3 g, 34 mmol) and 4-chlorobenzonitrile (1.55 g, 11.2 mmol) was placed in Erlenmeyer flask and was irradiated under microwave for 25 min (high power 700 W). The completion of reaction was monitored by TLC. Then water (10 ml) was added into the reaction mixture. The precipitate obtained was filtered off, washed with water and dried under vacuum (30 °C) and recrystallized from 50% aqueous ethanol.

4.2 Synthesis of 4-morpholino benzamide (2)

4- Morpholino benzonitrile (6 mmol) in ethanol (25 mL) and aqueous 6 N sodium hydroxide solution (15 ml) and was cooled to 0°C. To the above solution, 30% H₂O₂ (20 mmol) was added and the reaction mixture was stirred at 40-50°C for 4 h. The completion of the reaction was monitored by TLC. The reaction mixture was then again cooled to 0°C, acidified with 3N H₂SO₄ solution. After evaporation of ethanol from the reaction mixture, the residue was
extracted with CH₂Cl₂, washed with water and the organic layer was dried over Na₂SO₄ and concentrated to get the desired intermediate 4-morpholino benzamide.

4.3.1 Synthesis of N-(2-hydroxynaphthalen-1-yl) (methoxy phenyl) methyl)-4-morpholino benzamide (3 a-k)

One pot synthesis of the title compounds was achieved by stirring a mixture of 4-morpholino benzamide (1.1 mmol), 4-substitutedbenzaldehyde (1 mmol), β-naphthol (1 mmol) and oxalic acid (0.1 mmol) as a catalyst, on magnetic stirrer at 125°C under solvent free condition for 8-24 min. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and recrystallized from ethanol (70%). The yield and melting point of the synthesized compound was recorded.

Spectral data and elemental analysis data of the synthesized derivatives is given below

4.3.1 Synthesis of N-(2-hydroxynaphthalen-1-yl) ((2-mercaptophenyl) methyl)-4-morpholino benzamide

IR (KBr, νmax in cm⁻¹): 3566 (NH₂ amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 2555 (S-H mercapto), 1680 (C=O amide), 1415 (C-N).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.93 (t, 4H, -CH₂ morpholine ring), 3.61 (t, 4H, -CH₂ morpholine ring), 4.71 (s, 1H, -OH phenolic), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D₂O exchangeable). Mol. Weight: 468, MS m/z: 468 (M). Anal. (C₂₉H₂₄N₂O₃) Calc C 73.99, H 5.77, N 6.03. Found: C 73.84, H 5.66, N 6.27.

4.3.2 Synthesis of N-(2-hydroxynaphthalen-1-yl) (hydroxy phenyl) methyl)-4-morpholino benzamide

IR (KBr, νmax in cm⁻¹): 3566 (NH₂ amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1639 (C=O amide), 1410 (C-N).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.11 (s, 3H, -CH₃ of Ar alkyl), 2.93 (t, 4H, -CH₂ morpholine ring), 3.61 (t, 4H, -CH₂ morpholine ring), 4.71 (s, 1H, -OH phenolic), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D₂O exchangeable). Mol. Weight: 454, MS m/z: 455 (M+1). Anal. (C₂₉H₂₃N₂O₃) Calc C 74.34, H 5.77, N 6.16 Found: C 73.84, H 5.66, N 6.27.

4.3.3 Synthesis of N-(2-hydroxynaphthalen-1-yl)((p-tolyl) phenyl) methyl)-4-morpholino benzamide

IR (KBr, νmax in cm⁻¹): 3566 (NH₂ amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1639 (C=O amide), 1410 (C-N).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.60 (s, 3H, -CH₃ of Ar alkyl), 2.93 (t, 4H, -CH₂ morpholine ring), 3.61 (t, 4H, -CH₂ morpholine ring), 4.71 (s, 1H, -OH phenolic), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D₂O exchangeable). Mol. Weight: 470, MS m/z: 471 (M+1). Anal. (C₃₀H₂₃N₂O₃) Calc C 74.14, H 5.66, N 5.87. Found: C 74.14, H 5.66, N 5.87.

4.3.4 Synthesis of N-(furan-2-yl (2-hydroxynaphthalen-1-yl) methyl)-4-morpholino benzamide

IR (KBr, νmax in cm⁻¹): 3566 (NH₂ amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1639 (C=O amide), 1410 (C-N).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.93 (t, 4H, -CH₂ morpholine ring), 3.61 (t, 4H, -CH₂ morpholine ring), 4.71 (s, 1H, -OH phenolic), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.26 (d, 1H, -CH furan ring), 6.46 (d, 1H, -CH furan ring), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D₂O exchangeable). Mol. Weight: 466, MS m/z: 468 (M). Anal. (C₃₀H₂₃N₂O₃) Calc C 74.14, H 5.66, N 5.87.

4.3.5 Synthesis of N-(2-hydroxynaphthalen-1-yl)((2-hydroxyphenyl) methyl)-4-morpholino benzamide

IR (KBr, νmax in cm⁻¹): 3566 (NH₂ amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 2555 (S-H mercapto), 1639 (C=O amide), 1410 (C-N).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.93 (t, 4H, -CH₂ morpholine ring), 3.61 (t, 4H, -CH₂ morpholine ring), 4.71 (s, 1H, -OH β-naphthol), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D₂O exchangeable). MS m/z: 471 (M+1). Anal. (C₃₀H₂₃N₂O₃S) Calc C 74.67, H 5.57, N 5.95. Found: C 74.54, H 5.66, N 5.87. Mol. Weight: 470
sulphoxide (DMSO) to obtain a concentration of 5000 µg/ml. The compounds were screened for anti tubercular activity against 

4.3.9 Synthesis of N-((2-hydroxynaphthalen-1-yl) (4-nitrophenyl) methyl)-4-morpholino benzamide (3 g)
IR (KBr, ν max in cm⁻¹): 3566 (NH 0 amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1680 (C=O amide), 1415 (C-N), 765 (C-Cl). 

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.93 (t, 4H, -CH 2 morpholine ring), 3.61 (t, 4H, -CH 2 morpholine ring), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D2O exchangeable). Mol. Weight: 472, MS m/z: 473 (M+1). Anal. (C28H28ClN2O3) Calc C 71.24, H 5.56, N 5.87.

4.3.10 Synthesis of N-((2-hydroxynaphthalen-1-yl) (phenyl) methyl)-4-morpholino benzamide (3 j)
IR (KBr, ν max in cm⁻¹): 3566 (NH 0 amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1680 (C=O amide), 1415 (C-N), 765 (C-Cl).

4.3.11 Synthesis of N-((4-fluorophenyl)((2-hydroxynaphthalen-1-yl)methyl)-4-morpholinobenzamide (3 k)
IR (KBr, ν max in cm⁻¹): 3566 (NH 0 amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1680 (C=O amide), 1200 (C-F).

4.3.8 Synthesis of N-((2, 4-dichlorophenyl) (2-hydroxynaphthalen-1-yl)methyl)-4-morpholino benzamide (3 h)
IR (KBr, ν max in cm⁻¹): 3566 (NH 0 amine), 3250-3350 (O-H phenolic), 3094 (C-C Aromatic ring), 2950 (C-H Ar alkyl), 1680 (C=O amide), 1415 (C-N), 765 (C-Cl).

1H NMR (DMSOd6, 400 MHz) δ ppm: 2.93 (t, 4H, -CH 2 morpholine ring), 3.61 (t, 4H, -CH 2 morpholine ring), 5.51 (s, 1H, -OH β-naphthol), 5.82 (s, 1H, -CH Ar alkyl), 6.80-8.20 (m, 14H, Ar-H), 9.05 (s, 1H, -CONH, D2O exchangeable). Mol. Weight: 507, MS m/z: 508 (M+1). Anal. (C28H25Cl2N2O) Calc C 69.55, H 5.21, N 8.69. Found: C 69.64, H 5.66, N 5.87.
RESULTS AND DISCUSSION

Total 11 derivatives of N-((2-hydroxynaphthalen-1-yl) (substituted phenyl)methyl)-4-morpholino benzamide were synthesized and screened for their antibacterial activity using Tube Dilution Technique (Linezolid as a standard). Some of the synthesized compounds like 3b (R= 4-Hydroxy) have shown good activity against *S. aureus* and *B. subtilis*, 3g (R= 4-Chloro) and 3k (R= 4-Fluoro) have shown excellent activity against *S. aureus* and *B. subtilis* when compared with standard Linezolid. MIC values are given in Table 3.

### Table 3: Data of Antibacterial activity (MIC µg/ml)

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>S. aureus ATCC 6538</th>
<th>B. subtilis ATCC 6633</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>3b</td>
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<tr>
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<td>&gt;200</td>
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<tr>
<td>3f</td>
<td>&gt;200</td>
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<tr>
<td>3g</td>
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<tr>
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<td>≤ 50</td>
</tr>
<tr>
<td>Std (Linezolid)</td>
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<td>≤ 30</td>
</tr>
</tbody>
</table>

The result of antitubercular activity shows that compound 3h (R= 2, 4-Dichloro) has shown excellent antitubercular activity. Compound 3f (R= 2-hydroxy) has shown significant antitubercular activity. Compound 3i (R= 4-Nitro) has shown comparable antitubercular activity. All other compounds have shown satisfactory antitubercular activity when compared with the results obtained from standard. The result of antitubercular evaluation is given in Table 4.

### Table 4: Data of Antitubercular activity (MIC µg/ml)

<table>
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<tbody>
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<td>100</td>
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<tr>
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<tr>
<td>Rifampicin</td>
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</table>

CONCLUSION

Total 11 derivatives of N-((2-hydroxynaphthalen-1-yl) (substitutedphenyl) methyl)-4-morpholino benzamide 3(a-k) were synthesized as per the scheme reported. Structures of synthesized compounds were confirmed by spectral study such as IR, ^1^HNMR and Mass, Elemental analysis. The synthesized compounds were subjected to antibacterial and antitubercular evaluation. Some of the synthesized compounds like 3b (R= 4-Hydroxy) has shown comparable activity against *S. aureus* and *B. subtilis*, 3g (R= 4-Chloro) and 3k (R= 4-Fluoro) have shown excellent activity against *S. aureus* and *B. subtilis* when compared with standard Linezolid. The result of antitubercular activity shows that compound 3h (R= 2, 4-Dichloro) has shown excellent antitubercular activity. Compound 3f(R= 2-hydroxy) has shown significant antitubercular activity. Compound 3i (R= 4-Nitro) have shown comparable antitubercular activity. All other compounds have shown satisfactory antitubercular activity when compared with the results obtained from standard (Rifampicin).

The correlation of activity with the structure of synthesized derivatives, it has been observed that electron donating groups like 4-Chloro (3g), 2, 4-Dichloro (3h), 4-Fluoro (3k), attached to the phenyl ring increases antimicrobial activity. When the substituent Ar has electron donating groups such as 4-Hydroxy (3b), 2-Hydroxy (3f) showed moderate antimicrobial activity. The structure-activity relationship study showed that the morpholine ring is essential for antibacterial activity. The antibacterial activity may increase or decrease depending upon substituent Ar.
groups on aromatic ring. The structure -activity relationship revealed amide linkage (-CONH) to be essential for antitubercular activity.

The presence of two important moieties i.e. Morpholine and β-naphthol in the final derivatives containing –CONH-group have contributed towards better antimicrobial activity. Thus the designed N-((2-hydroxynaphthalen-1-yl)(substitutedphenyl)methyl)-4-morpholinobenzamide derivatives have shown significant antimicrobial activity.

From the research work undertaken and results obtained, it appears that, N-((2-hydroxynaphthalen-1-yl) (substituted phenyl) methyl)-4-morpholinobenzamide derivatives possess very good potential for antimicrobial activity and they can be developed as potent chemotherapeutic agents.

Acknowledgement
Authors are grateful to Mrs. Fatima Rafiq Zakaria, Chairman Maulana Azad Education Trust and Principal Dr. M.H. Dehghan, for providing the necessary facilities to carry out this work.

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